REMARKS

Status of the Claims

Claims 1-3, 8-13, 16, 39-40, 42, and 44 were previously cancelled. Claims 4, 14, 15, and 17-20 are cancelled by this amendment without prejudice.

Claims 21-23 and 30-38 stand withdrawn pursuant to the restriction requirement.

Applicant expressly preserves the right to pursue any of the foregoing claims in a subsequent continuation or divisional application.

The allowance of claims 5-7 is noted with appreciation.

Claim 24 is amended herein, claims 25-26 are amended for clarity, and new claims 45-47 are added, the new claims finding support in Table 2 at page 23 of the application as originally filed, with claim 47 finding further support at the results of the BIAcore™ assay given in the Examples, in particular see Example 2 ii at page 22.

Claims 41 and 43 are amended to no longer depend from claim 14, now cancelled.

The claims under consideration at this time are claims 5-7, 24-29, 41, 43, and 45-47.

The withdrawal of various previous rejections and objections as noted in paragraphs 5-12 of the Office Action is noted with appreciation.

Claim rejections – 35 U.S.C. § 112 first paragraph

The rejection of claims 24-29 as failing to comply with the written description requirement is respectfully traversed. Independent claim 24 has been amended herein for clarity. As now presented, claim 24 encompasses a genus of antibody fragments comprising Fab or Fab' fragments wherein the heavy and light chains are not covalently bonded to one another, and wherein one effector molecule is attached to an interchain cysteine of C_L and another effector molecule is attached to an interchain cysteine of C_H1, each of those two effector molecules being selected from a PEG or a PEG derivative. The Examiner's statement starting at the bottom of page 3 and continuing on the top of page 4 of the Action that the "…..the heavy and/or light chain further comprises an additional cysteine attached to an effector molecule" is respectfully not understood.

However, we trust that the presently amended claim deals with the Examiner's concerns as it clearly specifies where each effector molecule is attached. In the event the Examiner's concerns have not been addressed the Examiner is requested to explain further the objection.

The Examiner's attention is directed to Example 1, wherein various methods of making a tri-PEGylated Fab' fragment are disclosed. The PEG effector molecules are attached at the interchain cysteine of C_L, the interchain cysteine of C_H1, and at the hinge region. The extent to which a PEG molecule attaches at all three locations was found to depend on the nature of the reductant used, with TCEP reductant resulting in about 65% multi-PEGylation, and the other reductants resulting in substantially less multi-PEGylation. The extent of multi-PEGylation in each sample was determined by HPLC. The fact that thiol based reductants were less effective than TCEP reductant does not mean that multi-PEGylated antibody fragments are not enabled. To the contrary, such multi-PEGylated antibody fragments are fully described, and Example 1 shows that a good way to produce them is by using TCEP reductant, as illustrated in FIG. 1, such that the applicants were in possession of the claimed invention at the time of the application. See also the discussion at pages 15-16 of the specification. Accordingly, it is respectfully requested that the rejection of claims 24-29 under 35 USC § 112, first paragraph, be withdrawn.

Claim rejections – 35 U.S.C. § 102

Claim 4 was rejected under 35 USC 102(b) as being anticipated by Carter as evidenced by Bodmer et al. As claim 4 is now cancelled, this ground of rejection is rendered moot.

Claims 14-15, 17-19, 41 and 43 were rejected under 35 USC 102(b) as being anticipated by Hsei. Claims 14-15 and 17-19 are now cancelled; claims 41 and 43 are now dependent on claim 24, not claim 14. Accordingly, this ground of rejection is also rendered moot.

Claim rejections – 35 U.S.C. § 103

Claims 24-29 stand rejected under 35 U.S.C. 103 as obvious over Singh et al. as the primary reference in view of Hsei et al. and Humphreys. The rejection is respectfully traversed.

Claim 24 recites antibody fragments that have at least two or more effector molecules attached thereto, one effector molecule being attached to an interchain cysteine on each of the C_L and C_H1 regions, which two effector molecules are either PEG or a derivative thereof.

Singh et al. teaches a method of labeling **whole antibodies**, with non-selective selenol-catalyzed reduction employing labels such as biotin or a small molecule. This resulted in the addition of seven labels in less than 5 minutes.

Yet as discussed in the introduction of present application at page 1:

"*Random attachment* [in the prior art] *is often achieved through amino acids such as lysine and this results in effector molecules being attached at a number of sites throughout the antibody .....and this can lead to loss of activity.... and /or loss of affinity*".

Biotinylation of antibodies is known to have the potential to detrimentally affect the properties of the labeled antibodies. Therefore, detection methods have been developed to avoid the need to biotinylate antibodies.

Furthermore, labeling a whole antibody has different considerations compared to joining an effector molecule to a Fab or Fab' fragment. Because the whole antibody has a greater area (in particular constant region) over which the labels may be distributed, the properties of the whole antibody may be less affected by the process than a Fab or Fab' fragment would be.

Furthermore, small labels such as biotin (which has the formula $C_{10}H_{16}N_2O_3S$) or other small molecules have different properties than polymers such as PEG with an average molecular weight in the range 5,000 to 30,000Da. Thus it is respectfully submitted that the teaching of Singh et al is not relevant to the presently claimed invention. Nor does it teach or suggest to a skilled person the presently claimed fragments, in particular it does not teach a way of retaining affinity.

Hsei contains generic language indicating that a "conjugate" may comprise one or more polymers. However in certain specific embodiments Hsei teaches either that only one polymer molecule can be attached to a Fab, Fab' or Fab'-SH fragment, see page 23, lines 9-11, or alternatively in the specific situation of a $F(ab')_2$ that two polymer molecules can be attached on the heavy and light chains and as long as the corresponding heavy or light chain cysteine is replaced with a serine.

There is no suggestion from Hsei that a Fab or Fab' fragment wherein the heavy chain in the fragment is not covalently bonded to the light chain may be linked to two or three polymer molecules, and that the final molecule retains *in vitro* affinity and/or stability. In fact, the Examiner has cited to no refernce before the earliest priority date of the present application suggesting to a skilled person that an unlinked fragment would have sufficient attraction to support one PEG molecule on the light chain and another PEG molecule on the heavy chain without being pulled apart.

At the time of the priority date of the present invention, one skilled in the art would not have attempted to attach PEG (or a derivative) to the interchain cysteines of a Fab or Fab' fragment because of the risk that the PEG would draw water away from the antibody fragment, creating a destabilizing effect on the fragment that would force the heavy and light chains apart. The inventors herein discovered that, surprisingly, and contrary to prior perceptions in the art, an antibody fragment can be provided with PEG effector molecules attached to the interchain cysteines, and the heavy and light chains remain associated with each other, such that the PEGylated antibody Fab' fragment has equivalent antigen binding and *in vivo* activity compared to PEGylated Fab' fragments in which the interchain disulphide bond is present.

Combining Singh with Hsei would produce either a full antibody with seven PEG molecules attached (if that would work), or a Fab or Fab' fragment with only one label such as biotin or another small molecule, such that the combination of Singh and Hsei does not provide the presently claimed invention.

Humphreys WO99/15549 is concerned with the production of dimeric $F(ab')_2$ fragments containing a specific hinge sequence having four cysteines, particularly **dimeric** $F(ab')_2$ fragments containing the hinge sequence TCPPCPXYCPPCPA . Humphreys discloses fragments in which **both** interchain cysteines have been replaced

with serines. Humphreys makes no mention of fragments in which both the interchain cysteines were retained and have effector molecules attached. Thus combining Singh, Hsei, and Humphreys would not result in the structure of claim 24, namely a fragment having PEG attached to **both** its interchain cysteines, and there is no teaching or suggestion in the combined art to create such a structure.

As the Examiner correctly notes, the test of obviousness is what the combined teaching of these references would have suggested to those of ordinary skill in the art at the time the invention was made. Given the difficulty in preparing multi-PEGylated fragments, as illustrated by Figure 1, it is respectfully submitted that generic disclosures saying that the fragment may comprise an effector molecule does not teach a skilled person how to prepare the specific fragments recited in claims 24-29.

In fact there is no specific motivation from a combination of any of Singh, Hsei and Humphreys to provide the presently claimed fragments.

The fact that Singh had success in labeling antibodies with biotin does not necessarily mean that the applicants would have had the same success in labeling antibodies with PEG or PEG derivatives. The data in FIG. 1 show that success was not found for all reductants; instead, the inventors had to carefully determine which reductants would give them the desired multi-PEGylation.

To the extent that the Examiner notes that some degree of predictability is required, the fact that the applicants had to try several reductants before finding one that would work shows that this is an unpredictable art.

The rejection of claim 4 as obvious over Hsei et al. in view of Humphreys is now moot in view of the cancellation of claim 4.

In view of the foregoing, it is respectfully requested that the rejection under 35 USC 103 be withdrawn.

Double Patenting

Claims 4, 14-15, 17-19, 41 and 43 were rejected on the ground of non-statutory obviousness-type double patenting over claims 7 and 10 of U.S. 6,642,356 in view of

Hsei. Of these rejected claims, only claims 41 and 43 remain in the application, and these claims now depend only from claim 24, which is not rejected for double patenting. It is therefore respectfully submitted that the double patenting rejection has been overcome.

Claim Objections

Claim 41 was objected to as failing to further limit base claim 14 from which it (multiply) depended. As claim 41 now depends only from claim 24, and not from claim 14, it is submitted that this objection has been overcome.

Claim rejections – 35 USC § 112 second paragraph

Claim 18 was rejected as indefinite with regard to certain phraseology therein. As claim 18 is now cancelled, this ground of rejection is moot.

Claims 14-15, 17-20, 24-29, 41 and 43 were rejected as indefinite with respect to the use of the term "derivative." As claims 14-15 and 17-19 have been cancelled, this rejection now applies only to claims 24-29 and 41-43. With regard to the term "derivative," the Examiner is respectfully referred to page 8, lines 4-9 of the specification as filed, wherein the term "derivative" as used in this application is defined. It is respectfully submitted that this definition is sufficient to apprise one of skill in the art of the metes and bounds of the claim, such that this ground of rejection is overcome.

As all points of rejection have been overcome, a Notice of Allowance is respectfully requested. The Examiner is invited to contact the applicant's undersigned representative if it is believed that a conference might further the prosecution of this matter.

Respectfully submitted,

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